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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/801,956	FUJIMOTO ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-8, 10, 12-13, 17-19, 21, 26-28, 30, 35-37, 39, 44-47, 49, 52-53, 58-61, 63, 74, and 81-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-3,5-8,10,12,13,17-19,21,26-28,30,35-37,39,44-47,49,52,53,58-61,63,74 and 81-96.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/19/2007 has been entered.

The papers of 11/29/2007 has amended claims 1-3,6, 17, 26, 35, 44, 58, 72, 84, 88, 93 and 96. Claims 4, 9, 11, 14-16, 20, 22-25, 29, 31-34, 38, 40-43, 48, 50-51, 54-57, 62, 64- 73, and 75-80 are canceled.

The written description rejection of claims 1-3 and 5 has been overcome by amending the claims to recite the markers D12S1657, D12S393, D12S1706, and D12S346.

The New matter rejection of claims 1-3, 5-8, 10, 12-13, 85, 87, 89, 91 and 95 are withdrawn due to the teachings of page 32, lines 22-27 of the specification in view of the arugments.

The 112 2nd paragraph rejection of claims 6-8, 10, 12-13, 17-19, 21, 26-28, 30, 35-37, 39, 44-47, 49, 52-53, 58-61, 63, 74, and 81-96 has been withdrawn as the claims are now of comprising language.

The amendment to claim 17 to require loss of heterozygosity of any of D12S1657, D12S393, D12S1706, and D12S346 indicates that the probability that the

subject is suffering from a metastatic cancer is higher than the subject is suffering from a primary cancer has overcome the 102 rejection of Soegnas, as Soegnas does not teaches prediction of suffering from a secondary tumor relative to a primary tumor.

The amendment to claim 26 to require loss of heterozygosity of any of D12S1657, D12S393, D12S1706, and D12S346 indicates that the probability that the subject is suffering from a progressing cancer is higher than the probability the subject is suffering from a non-progressing cancer has overcome the 102 rejection of Soegnas, as Soegnas does not teach determination of cancer progression based on LOH.

The amendment to claims 35 and 58 have overcome the 102 rejection of Soegnas because the amendments require predicting responsiveness or efficacy of biochemotherapy, which Soegnas does not teach.

The objection of claims 1-6 has been withdrawn in view of the amendment to correct the typographical error.

The 102 rejection of Soegnas of claim 74 has been withdrawn as the claim is dependent on claim 1, which Soegnas does not anticipate.

Claims 1-3, 5-8, 10, 12-13, 17-19, 21, 26-28, 30, 35-37, 39, 44-47, 49, 52-53, 58-61, 63, 74, and 81-96 are pending.

This action is in response to papers filed on 11/19/2007.

Claim Objections

2. Claims 6-8, 10, 12-13, 17-19, 21, 26-28, 30, 35-37, 39, 44-47, 49, 52-53, 58-61, 63, 74, and 81-96 are objected to because of the following informalities: Claims 6-8, 10, 12-13, 17-19, 21, 26-28, 30, 35-37, 39, 44-47, 49, 52-53, 58-61, 63, 74, and 81-96 are

objected to as it recites "LOH" but does not recite the full terminology for the acronym and the acronym may have alternative meanings.

3. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

5. Claims 26-28, 30, 44-47, 49, 52, 53, 85, 86 89 and 90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim 26 and all dependent claims are drawn to a method of monitoring melanoma or colon cancer progression recite in the last 2 lines "the probability for the subject to suffer from a progressing cancer is higher than the probability for the subject to suffer from a non-progressing cancer." The limitation of differentiating the probability of progressing cancers and non-progressing cancers is not suggested or described in the specification. The Applicants response asserts that pages 24 (lines 11-12) and 37 provide support for this limitation. Page 24 as suggested by the response

discusses the loss of these markers is indicative of a higher probability of metastastic cancer, than primary melanomas. Page 37 discusses disease outcome for melanoma based on the loss of the markers. However, neither of the cited sections refer to colon cancer nor suggest a comparison of progressing cancer vs. non-progressing cancers. Thus the specification provides no teaching or suggesting of "the probability for the subject to suffer from a progressing cancer is higher than the probability for the subject to suffer from a non-progressing cancer," and this appears to be new matter.

Claim 44 and all dependent claims are drawn to a method of determining the probability of survival and requires in the last line, " the subject has a low probability of survival if the subject is has not responded to biochemotherapy". The response asserts on page 13 section 5 that the specification provides support for the amendment on page 26, lines 12-15 and page 27. Pages 26 and 27 of the specification do not teach or suggest the limitation the subject has not responded to biochemotherapy. Thus the inclusion of this limitation is considered new matter.

Enablement

6. Claims 1-3, 5-8, 10, 12-13, 17-19, 21, 26-28, 30, 35-37, 39, 44-47, 49, 52-53, 58-61, 63, 74, and 81-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting melanoma or predicting efficacy of responsiveness of melanoma to adriamycin, or determining the probability of responsiveness to adriamycin in a human subject comprising: obtaining an accellular DNA from plasma or serum samples from a human subject, isolating accellular DNA, detecting the loss of D12S1657, D12S393, D12S1706, and D12S346 markers in the

accellular DNA, wherein the loss of the D12S1657, D12S393, D12S1706, and D12S346 indicates increased incidence of melanoma in human subjects or decreased efficacy of responsiveness to adriamycin, or probability of responsiveness to adriamycin, does not reasonably provide enablement for detecting one or more DNA Markers D12S1657, D12S393, D12S1706, and D12S346. The specification is not enabling for the correlation of the 12q22-23 region to specifically colon, melanoma or breast cancer. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

Claim 1 broadly encompasses a method of detecting DNA markers in accellular DNA samples.

Claim 6 encompasses a method of detecting melanoma in a human subject by providing a sample of accellular DNA, detecting in accellular DNA the loss of heterozygosity of any of f D12S1657, D12S393, D12S1706, and D12S346 is indicative of melanoma.

The claim thus encompasses to the staging of melanoma by the LOH of D12S1657, D12S393, D12S1706, and D12S346 in serum, plasma, urine, suptum, feces, etc.

Claim 17 encompasses a method of staging melanoma or colon cancer in a human subject by providing a sample of accellular DNA, detecting in accellular DNA the loss of heterozygosity of any of D12S1657, D12S393, D12S1706, and D12S346 is indicates that the probability that the subject is suffering from a metastatic cancer is higher than the subject is suffering from a primary cancer.

The claim thus encompasses to the staging of melanoma by the LOH of D12S1657, D12S393, D12S1706, and D12S346 in serum, plasma, urine, suptum, feces, etc.

Claim 26 encompasses a method of monitoring progression of melanoma or colon cancer in a human subject by providing a sample of accellular DNA, detecting in accellular DNA the loss of heterozygosity of any of f D12S1657, D12S393, D12S1706, and D12S346 is indicates that the probability that the subject is suffering from a progressing cancer is higher than the subject is suffering from a non-progressing cancer.

The claim thus encompasses to the monitoring of melanoma or colon cancer by the LOH of D12S1657, D12S393, D12S1706, and D12S346 in serum, plasma, urine, suptum, saliva, feces, etc.

Claim 35 encompasses a method of predicting the efficacy of melanoma biochemotherapy in a human subject by providing a melanoma tissue sample or body fluid sample containing DNA prior to administration of biochemotherapy, detecting in accellular DNA the loss of heterozygosity of any of f D12S1657, D12S393, D12S1706, and D12S346 is indicates poor efficacy of biochemotherapy in the subject.

The claim thus encompasses to the efficacy of melanoma biochemotherapy by the LOH of D12S1657, D12S393, D12S1706, and D12S346 in a melanoma tissue sample or any bodily fluid which broadly includes: serum, plasma, urine, sputum, etc.

Further the claims broadly encompass "any" biochemotherapy and responsiveness to any number of rounds of therapy.

Claim 44 encompasses a method of determining survival in a human subject suffering from Stage III or IV melanoma by providing a sample of accellular DNA, detecting in accellular DNA the loss of heterozygosity of any of f D12S1657, D12S393, D12S1706, and D12S346 is indicates that the subject has a low probability of survival if the subject is has not responded to biochemotherapy.

The claim thus encompasses to the determining survival of human subject with stage III or IV melanoma by the LOH of D12S1657, D12S393, D12S1706, and D12S346 in serum, plasma, urine, sputum, etc.

Further the claim is drawn to predicting "any" survival. Thus is directed to predicting of the subject will die due to heart attack, collision injury, stroke, etc based solely on the LOH of D12S1657, D12S393, D12S1706, and D12S346.

Claim 58 encompasses a method of determining probability of responsiveness to a melanoma biochemotherapy by providing a melanoma tissue sample or bodily fluid , detecting in the DNA the loss of heterozygosity of any of f D12S1657, D12S393, D12S1706, and D12S346 is indicates that the subject has a low probability of responsiveness to biochemotherapy.

The claim thus encompasses to determining the efficacy of responsiveness to melanoma biochemotherapy by the LOH of D12S1657, D12S393, D12S1706, and D12S346 in a melanoma tissue sample or any bodily fluid which broadly includes: serum, plasma, urine, sputum, etc.

Claim 93 encompasses a method of detecting colon or breast cancer by detecting LOH of D12S1657, D12S393, D12S1706, and D12S346 in cancer tissue or bodily fluids, wherein LOH of the markers is indicative of breast cancer, primary colon cancer, or metastastic colon cancer.

The amount of direction or guidance and the Presence and absence of working examples in the specification.

The specification teaches detection of D12S1657, D12S393, D12S1706, and D12S346 for diagnosis of melanoma, breast, or colon cancer. The specification sets forth no other uses for the claimed invention.

The specification teaches there is an unexpected LOH of markers for 12q22-23 in accellular samples (see page 3, lines 5-8). The specification further teaches that the 12q22-23 region encompasses the APAF-1 locus (see page 9, line 26) and there was a statistically significant allelic imbalance in metastatic tumors and primary melanoma ($p=0.02$)(see page 9, lines 28-29). Further APAF-1 loss was significantly correlated with a worse prognosis ($p<0.05$) (see page 10, 1st line). The specification further teaches melanoma patients that responded to chemotherapy had a significantly lower frequency of allelic imbalance at 12q22-23 ($P<0.029$) and better prognosis ($p<0.046$) (see page 10 line 12-13), then patients with an allelic imbalance. Further the specification teaches the use of 12q22-23 markers: D12S1657, D12S393, D12S1706, and D12S346.

The specification teaches LOH frequencies in primary melanomas tissue samples were 20%, 31%, 13% and 17% at D12S1657, D12S393, D12S1706, and D12S346, respectively (see table 1). The specification teaches LOH frequencies in metastatic melanomas were 23%, 35%, 17% and 21% at D12S1657, D12S393, D12S1706, and D12S346, respectively (see table 1). The specification asserts that there is a higher frequency of allelic imbalance in metastatic melanoma than primary melanoma ($P=0.02$), although there is no frequency differences between stage III melanoma and stage IV melanoma (see page 24,line 11 to page 15 line 1).

The specification further teaches there is no correlation between APAF-1 status and overall survival in primary melanoma tissue samples, but there is a statistically significant correlation between APAF-1 status and Stage III/IV melanoma ($p=0.05$) (see page 26, lines 10-15). Further survival of stage III metastatic melanoma and stage III

metastatic melanoma with RLM was statistically correlated with APAF-1 status (P=0.03, p=0.02) but metastatic melanoma with ILM was not (p=0.17) (see page 26 line 25-page 26 line 3). It thus appears that LOH of D12S1657, D12S393, D12S1706, and D12S346 is correlated with survival of patients with stage III metastatic melanoma with RLM, but not survival with stage III metastatic melanoma with ILM. The specification is silent on LOH of D12S1657, D12S393, D12S1706, and D12S346 and stage IV melanoma.

Further the specification teaches the effect of allelic 12q22-23 in serum samples on melanoma patient outcomes. The specification teaches a significant relationship of allelic imbalance of D12S1657, D12S393, D12S1706, and D12S346 markers (p=0.029) before chemotherapy in the responder group (5 of 24), but not in the responder group after chemotherapy (9 of 24) (see page 36, line 11-15). It thus appears that chemotherapy resulted in 4 subjects having an LOH of the recited alleles in response to the biochemotherapy (see page 36, line 11-15). While 11 of 20 the non-responders had allelic imbalance before therapy, while only 7 of the 20 had allelic imbalance after therapy(see page 36, line 11-15). These teachings suggest that in 4 non-responders allelic imbalance can be restored in response to biochemotherapy.

Further patients with D12S1657, D12S393, D12S1706, and D12S346 LOH had a statistically significantly worse survival rate (p=0.046) (see page 36, line 17) than allelic imbalance negative subjects. The specification teaches response to chemotherapy was related to survival (p<0.001) (see page 36, line18).

The specification teaches only concurrent BC regimen of dacarbazine(DTIC), cisplatin, vinblastin, interferon .alpha.-2b, IL-2, and tamoxifen (see page 31, lines 13-17).

The specification further teaches in table 6, D12S1657, D12S393, D12S1706, and D12S346 LOH occur in no colon adenomas, 21% of primary colon cancers, or 54% of colon cancer derived liver metastases. Further the specification teaches in table 7, there are a D12S1657, D12S393, D12S1706, and D12S346 LOH in 25% of primary breast cancers. However the specification does not teach that the D12S1657, D12S393, D12S1706, and D12S346 LOH are statistically correlated with colon cancer or breast cancer. Further the specification provides no suggestion or support of where the samples of tables 6 and 7 were obtained. It thus is assumed these sample were from primary tumor samples.

The specification teaches in Table 6 that of 33 colon adenomas none had LOH of the markers, only 9 of 42 primary colon cancers LOH, while 15 of 28 liver metastases from colon cancer had LOH (see table 6). Thus the specification teaches LOH of the markers does not predictably detect colon cancer or metastases, as of 103 cancer patients only 24 would have been identified as cancer patients.

The specification further teaches that in table 7 that of 28 patients with primary breast cancer only 7 had LOH. Thus it would be unpredictable to use LOH to detect breast cancer as 21 patients would incorrectly be identified as cancer free.

The specification does not teach a statistically significant relationship between any cancer other then melanoma and 12q22-23 LOH.

The specification does teach a statistical relationship between LOH of D12S1657, D12S393, D12S1706, and D12S346 and breast or colon cancer. The specification does not teach that the markers for 12q22-23 are markers of APAF-1.

The specification does teach a statistically significant association of 12q22-23 LOH and melanoma, therapeutic response and outcome, but the specification teaches there is not a statistically significant relationship after chemotherapy, making the marker unpredictable for melanoma in those cases.

The specification does teach D12S1657, D12S393, D12S1706, and D12S346 are associated with melanoma and its progression and outcome. The specification teaches that the recited markers are associated with melanoma and response, before but not after chemotherapy. The specification further teaches the recited markers correlate with survival of type III melanoma with RLM, but not ILM. The specification teaches only D12S1657, D12S393, D12S1706, and D12S346 markers of 12q22-23. The specification does not teach a statistical relationship of recited markers with a cancer other then melanoma in subjects other than humans.

Although the specification teaches LOH of D12S1657, D12S393, D12S1706, and D12S346 in de-proteinized blood is correlated with the incidence and progression of melanoma, the specification provides no support that LOH of the recited alleles in urine, sputum, sperm, etc is correlated with melanoma, breast cancer, or colon cancer. The specification teaches," it has been established that markedly increased concentrations of soluble DNA are present in plasma of individuals with cancer and some other diseases, indicating that cell free serum or plasma can be used for detecting

cancer DNA with microsatellite abnormalities" (see page 8, lines 10-15). The specification appears to suggest that the accellular DNA is released into the serum or plasmid, however it does not teach or suggest the DNA from melanoma, breast or colon cancer would be present in sperm, feces, sputum, etc. It would thus be unpredictable to make such an association.

The state of prior art and the predictability or unpredictability of the art:

The prior art teaches that LOH D12S1657, D12S393, D12S1706, and D12S346 is common in metastatic melanoma (see abstract, Soegnas, et al Nature, 2001, vol 409, 207-211). The prior art teaches D12S1657, D12S393, D12S1706, and D12S346 LOH is indicative of poor response to chemotherapy, (see page 209, column 1, lines 8-10). The prior art does not teach a correlation between D12S1657, D12S393, D12S1706, and D12S346 LOH and any cancer other than melanoma.

The prior art does not teach D12S1657, D12S393, D12S1706, and D12S346 LOH is associated with "any" cancer other then melanoma.

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such

irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to establish that a predicative relationship exists between LOH of D12S1657, D12S393, D12S1706, and D12S346 and melanoma, colon cancer, or breast cancer. Experimentation would be replete with unpredictable trial and error analysis because the specification does not teach LOH of D12S1657, D12S393, D12S1706, and D12S346 is associated with colon or breast cancer, however the specification does teach melanoma is associated with the loss of D12S1657, D12S393, D12S1706, and D12S346. However, the specification teaches that the recited markers are lost in 4 melanoma subjects that responded to biochemotherapy following chemotherapy, but 4 melanoma subjects that did not respond regain heterozygosity. Thus it appears that loss or retention of heterozygosity of the markers is unpredictable after biochemotherapy. The specification teaches D12S1657, D12S393, D12S1706, and D12S346 are not predictive of survival in type III melanoma with ILM. As these markers can be lost or gained with chemotherapy and are not predictive of survival with type III melanoma with ILM they are not predictable

markers in colon or breast cancer in subject, or even "any" melanoma. The art confirms melanoma is associated with LOH of markers: D12S1657, D12S393, D12S1706, and D12S346, but one of skill in the art would have to recruit an enormous population of ethnically diverse subjects with colon or breast cancer and cancer-free controls and determine the association of loss of D12S1657, D12S393, D12S1706, and D12S346 with colon or breast cancer to determine a predictive relationship exists.

Further the skilled artisan would have to determine if loss of D12S1657, D12S393, D12S1706, and D12S346 in accellular DNA in feces, sperm, urine, sputum etc. is indicative or diagnostic of anything. It would be unpredictable in that the specification only teaches the accellular DNA isolated from blood, serum or plasma samples in relation to melanoma. The art nor specification provide any evidence that acellular DNA from urine, sperm, feces, etc would come in contact with the cancer cells in such a way that it could contain DNA released from the tumor and thus result in the outcomes predicted by the claims.

The skilled artisan would have to determine for claim 17, how a patient could be suffering from metastatic cancer, but not a primary cancer. This would be unpredictable as it is accepted in the art that primary tumors are precursor of metastatic tumors. Thus it is unpredictable how a subject can have a higher probability of a metastatic tumor than a primary tumor.

Further the artisan would have to determine if loss of D12S1657, D12S393, D12S1706, and D12S346 is indicative of increased probability of a progessing tumor compared to a non-progressing tumor. This would be unpredictable in that the

specification only provides support for the loss of the markers being correlated with progressing tumors, but does not provide a comparison or analysis with respect to non-progressing tumors. Thus it would be unpredictable to make such an association without data.

Independent claim 6 and 93 demonstrate that the method claim is unpredictable. Claim 6 is drawn to the detection of melanoma in a subject by analyzing loss of heterozygosity in accellular DNA. Claim 93 is drawn to the detection of breast or colon cancer by detecting LOH in bodily fluids, which encompasses blood, plasma, or serum from which the method of claim 6 gets its accellular DNA. Thus analysis of the claims suggests that one cannot predictably determine if a human subject has melanoma, breast, or colon cancer by LOH of the recited markers in accellular DNA, as the claims clearly state that the LOH is indicative of all 3. Further as discussed above only 24 of 103 colon cancer patients had LOH, thus allowing 79 subjects to be misidentified as cancer free by this claim. Further only 25% of breast cancer patients had LOH, thus this would allow 21 breast cancer patients to be identified as cancer free.

Further it would be unpredictable to associate a poor efficacy of treatment to "any" biochemotherapy by loss of D12S1657, D12S393, D12S1706, and D12S346. It would be unpredictable as the specification teaches that allelic imbalance changes in response to biochemotherapy. It thus appears that chemotherapy resulted in 4 subjects having an LOH of the recited alleles in response to the biochemotherapy (see page 36, line 11-15). While 11 of 20 the non-responders had allelic imbalance before therapy, while only 7 of the 20 had allelic imbalance after therapy(see page 36, line 11-15).

Further the claims are not limited to the therapies taught in the specification, but "any" therapies and any number of rounds of therapy. It would be unpredictable to associate the outcomes of treatment with any biochemotherapy or multiple rounds of biochemotherapy as the specification merely teaches a single round of therapy with The specification teaches only concurrent BC regimen of dacarbazine (DTIC), cisplatin, vinblastin, interferon .alpha.-2b, IL-2, and tamoxifen (see page 31, lines 13-17).

Further it would be unpredictable to stage melanoma by the loss of D12S1657, D12S393, D12S1706, and D12S346 in accellular DNA when the specification nor art provide support for such a correlation. The specification merely teaches staging melanoma by loss of D12S1657, D12S393, D12S1706, and D12S346 in melanoma tissues. The specification nor art suggest that a similar correlation is observed in accellular DNA. Further as discussed above accellular DNA is a broad genus and the specification is only enabling of accellular DNA isolated from blood, plasma, or serum.

Further it would be unpredictable to determine survival in melanoma patients based solely on D12S1657, D12S393, D12S1706, and D12S346. Survival is based not only on cancer progression, but other health conditions, as well as traumatic injury, suicide, etc. The specification appears to suggest that the loss of the markers in accellular DNA from blood, plasma, or serum is predictive of melanoma survival, but not "any" survival.

Due to the scope of the claims, one of skill in the art would be required to further undertake extensive trial and error experimentation to first determine a predictive

relationship between loss of "any" D12S1657, D12S393, D12S1706, and D12S346with melanoma, colon, or breast cancer to determine a predictive relationship exists.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

The response asserts that the claim 1 is enabled. This argument has been reviewed but is not considered persuasive as the enablement requires the specification to teach how to make and use the invention as claimed. While, the specification teaches how to make the claimed invention, it does not adequately provide support for the use of the invention to detect breast cancer, colon cancer and melanoma as described above.

The response asserts that claim 6 is enabled as the examiner apparently assumed the responders were melanoma free. This argument has been thoroughly reviewed and the examiner concurs that the claims do not require that the responders be melanoma free and the specification (Table 4 and page 31, line 19-page 32, line 9) provides support for several levels of response as depicted in the arguments. The examiner still asserts the claims are not enabled for the scope of "any" accellular DNA as described above. Further the fact that the claims are presented that encompass the detection of breast cancer, colon cancer, or melanoma is bodily fluids or accellular DNA

demonstrates that it is unpredictable to detect any of the 3 individually, thus the artisan might be able to determine if LOH of the markers is associated with one of the three types of cancer, but could not detect which of the 3 cancers is present as the claims require.

The response asserts that the specification is enabling for claims 17 and 26. The response specifically asserts that LOH of DNA markers was higher in metastatic melanoma or colon cancer than in primary melanoma or colon cancer and points to pages 24 and 37. However, the claims are drawn to staging or monitoring progression melanoma or colon cancer, which is not taught in the specification. As both the primary and metastatic tumors have LOH it would be unpredictable to determine the stage based on LOH. Further the specification does not provide support for a correlation with melanoma or colon cancer in "any" bodily fluid as discussed above.

The response further asserts claims 35 and 58 are enabled. The response asserts that the claims require "prior to administration of biochemotherapy." The examiner concurs that prior to administration of biochemotherapy is a limitation of the claim, however the claims do not limit it to prior only to an initial round of therapy as discussed above, nor do the claims, specification or art demonstrate that the loss of D12S1657, D12S393, D12S1706, and D12S346 are predictive of response or efficacy of "any" biochemotherapy. Further as previously discussed the claims are drawn to detection of the markers in any "bodily" fluid which is not enabled.

The response asserts that claim 44 is enabled as the examiner had an erroneously asserted the specification is silent on stage IV and LOH. The response

further asserts the specification teaches the stage III melanoma with RLM was statistically correlated with APAF-1 status. The response further asserts that LOH of DNA markers in stage III/IV melanoma was significantly associated with decreased overall survival and suggests support on page 26, lines 12-15. These arguments have been thoroughly reviewed but are not considered persuasive as the indicated part of the specification merely describes the loss of APAF-1 not all of the recited markers the claims require. Thus the specification does not teach and thus is not enabled for the detection of D12S1657, D12S393, D12S1706, and D12S346 in the probability of survival as figure 2 clearly demonstrates that the APAF1 gene is between markers D12S1706 and D12S346 and thus could be lost without affecting LOH of the claimed markers. Further as previously discussed the claims are drawn to detection of the markers in any "bodily" fluid which is not enabled.

The response asserts that claim 93 is enabled. The response asserts that the examiner was incorrect in the assertion that the control DNA was obtained from the patients peripheral blood lymphocytes. The response asserts, "contrary to the Examiner's assertion that the specification does not teach use of peripheral blood lymphocytes as a control (page 6, lines 1-3 of the Office Action), the specification states at page 32, lines 27-29 "[c]ontrol DNA for each melanoma patient[s] was obtained from the respective peripheral blood lymphocytes." These arguments have been thoroughly reviewed but are not considered persuasive as the response has pointed to where the control DNA was obtained for the melanoma patients, but provides no support for the

breast cancer or colon cancer controls. Further the specification teaches colon adenomas had no LOH, thus the LOH is not predictive of any primary colon cancer.

The response further asserts that the LOH of breast cancer and colon cancer control cells was 0% on the control DNA as demonstrated by figure 6. This argument has been reviewed put is not considered persuasive as figure 6 appears to be studies of melanoma before and after biochemotherapy and thus does seem to be relevant to the claim 93,as it is drawn to coon or breast cancer. Further as previously discussed the claims are drawn to detection of the markers in any "bodily" fluid which is not enabled.

The response further asserts that the Examiner's comment that the 12q22-23 region is much larger than APAF-1, applicants respectfully submit that the APAF-1 status was determined by analysis of DNA markers D12S1657, D12S393, D12S1706, and D12S346 encompassing the 12q22-23. This argument has been reviewed but is not considered persuasive APAF-1 could be lost without affecting the markers of the claims. It would be unpredictable to associate the deletion of a gene by the loss of a single marker that is near the gene, detection of the presence or absence of the gene or a marker within the gene is required.

The response asserts that the tables 6 and 7 are drawn to LOH in acellular DNA in contrast to the examiners assertion they are drawn to biopsies. The response points to the page 32, lines 22-29 as support. The cited part of the specification does not suggest or mention breast cancer or colon cancer, but describes the experimental procedure for the melanoma patients before and after therapy. Thus this appears to be argument not proof, thus the argument is not persuasive.

The response further correctly denotes the claims have been amended to require human subjects and the examiner concurs.

The response further asserts that figure 7 demonstrates that chemotherapy does not result in LOH as exemplified in the non-responders. This argument has been thoroughly reviewed but is not considered persuasive because patients 33-35 do have LOH in response to chemotherapy and thus agrees with examiners argument, that chemotherapy alters retention or loss of the markers of interest.

The response further asserts that loss of the DNA markers is not required to result in melanoma, breast or colon cancer, but must be a marker. While the examiner agrees with these arguments, the specification is not enabled for the breadth of the claims as discussed in detail above.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 17-19, 21 83 and 84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims require in the lat three lines, "probability for the subject to be suffering from a metastatic cancer is higher than the probability for the subject to be suffering from a primary cancer." It is unclear how a subject could suffering from a metastatic cancer without a primary tumor. It is thus unclear how one could predict a subject has a higher probability of metastatic cancer.

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1,5, 6, 10, 12, 13, 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Soengas, et al (Nature, 2001, volume 409, pages 207-211).

As the specification does not specifically state a definition of acellular DNA, acellular DNA is given its broadest reasonable interpretation of any DNA not contained in a cell, including DNA isolated from a cell, tumor, etc. The DNA isolated from a primary tumor sample will inherently comprise acelullar DNA as the removal of the tumor will contain DNA from blood and tissue that has been released as part of obtaining the sample. Thus the sample has DNA that exists as acelullar DNA in the subject.

With regards to claim 1, Soengas et al teaches detection of loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 markers in 24 tumors from patients using 6 12q22-23 microsatelite markers (see figure 1 and legend). Soegnas thus teaches a method of providing a sample containing DNA from a human subject and detecting one or more DNA markers. As the samples of Soegnas as from tumor samples, they comprise DNA that is extraceullar.

With regards to claim 5, Soegnas teaches the use of markers encompassing the APAF-1 locus (see page 207, 2nd column, lines 17-19).

With regards to claim 6, 13, Soegnas teaches loss of APAF1 and micro satellite markers D12S1657, D12S393, D12S1706, and D12S346 in patients are detected in metastatic melanoma (see abstract; page 207 2nd column, lines12-14). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR. As the samples of Soegnas as from tumor samples, they comprise DNA that is extraceullar.

With regards to claim 10, Soegnas teaches the use of markers encompassing the APAF-1 locus (see page 207, 2nd column, lines 17-19).

With regards to claim 12, Soegnas teaches detection of APAF-1 in primary melanoma cells.

With regards to claim 17, Soegnas teaches there is a high rate of APAF-1 LOH in metastatic melanoma (see page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Soegans thus teaches LOH of APAF-1 in melanoma indicates a high probability of metastatic cancer.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 35, 39-40, 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soegnas, et al (Nature, 2001, volume 409, pages 207-211).

With regards to claims 35,39, 40, Soegnas teaches there is correlation of APAF-1 levels and response to adriamycin in melanoma cells (see page 209, column 1, lines

8-10). Soegans teaches that APAF-1 levels are lower in melanoma's due to APAF-1 LOH. Soegnas teaches detection of LOH for markers D12S1657, D12S393, D12S1706, and D12S346 (see figure 1B). Soegnas thus teaches APAF-1 LOH results in poor efficacy of treatment in melanoma.

With regards to claim 58, Soegnas teaches assessment of APAF1 status improves therapeutic management for patients, as it is a required for apoptosis and thus a marker of chemosensitivity (see page 210, 2nd column, lines 20-26).

With regards to claim 59, Soegnas teaches LOH analysis from tumor samples (see page 210, 2nd column, analysis of APAF-1 locus).

Soegnas does not teach that loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 is predictive of response to biochemotherapy or predicted efficacy of response to biochemotherapy..

However, Soegans teaches "Assessment of Apaf-1status may therefore improve the therapeutic management of patients with malignant melanoma" (see page 210, 2nd column last line of text).

Therefore, it would be prima facie obvious to one of skill in the art at the time the invention was made to predict efficacy of response to adriamycin (a biochemotherapy) in patients or the probability of responsiveness to adriamycin in view of the teachings of Soegnas with a reasonable expectation of success. It would have been obvious to one of skill in the art in view of the teachings of Soegnas to use D12S1657, D12S393, D12S1706, and D12S346 to predict responsiveness or efficacy of treatment as Soegans teaches "Assessment of Apaf-1status may therefore improve the therapeutic

management of patients with malignant melanoma" (see page 210, 2nd column last line of text). The artisan would be motivated because Soegans suggest such a method as cited above.

Response to arguments

The arguments to Soegnas anticipating claims 35 and 58 are moot, as the rejection has been withdrawn and a 103 has been presented.

11. Claims 1-3, 5, 6-8, 10, 11, 12, 13, 35-37, 39, 58, 59-61, 63, 74 and 81-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soegnas, et al (Nature, 2001, volume 409, pages 207-211) in view of Gocke et al (US Patent 6156504).

As noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the present situation, steps of independent claims 1, 6, 17, 26, 35, and 58 are able to stand-alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language of the preamble to claims 1, 6, 17, 26, 35, and 58 merely sets forth the

intended use or purpose of the claimed methods, but does not limit the scope of the claims.

Soegnas et al teaches detection of loss of heterozygosity of 12q22-23 region in 24 patients using 6 12q22-23 microsatelite markers including D12S1657, D12S393, D12S1706, and D12S346 (see figure 1 and legend). Soegnas further teaches genomic DNA for tumor and normal cells were amplified by PCR.

Soegnas teaches loss of APAF1 and microsatellite markers in the 12q22-23 regions in patients are detected in metastatic melanoma (see abstract; page 207 2nd column, lines12-14). Soegnas further teaches genomic DNA for tumor and normal cells were amplified by PCR. This is being interpreted as isolating genomic DNA, thus making it acellular. Soegnas teaches detecting cancer by LOH of markers to 12q2-23.

Soegnas teaches there is a high rate of APAF-1 LOH in metastatic melanoma (see page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Soegnas thus teaches LOH of APAF-1 in melanoma indicates a high probability of metastatic cancer.

Soegnas teaches loss of APAF-1 is associated with disease progression (see page 208, lines 2-4).

Soegnas teaches there is correlation of APAF-1 levels and response to Adriamycin in melanoma cells (see page 209, column 1, lines 8-10). Soegnas teaches that APAF-1 levels are lower in melanomas with APAF-1 LOH. Soegnas thus teaches APAF-1 LOH results in poor efficacy of treatment in melanoma.

With regards to claim 58, Soegnas teaches assessment of APAF1 status improves therapeutic management for patients, as it is a required for apoptosis and thus a marker of chemosensitivity (see page 210, 2nd column, lines 20-26).

Soegnas does not teach the use of plasma (claims 3,8, 19, 28, 61), serum (2, 7, 18, 27, 60) , or blood (claims 81, 82, 84, 86, 90, 92, 96) as a sample.

However, Gocke et al teaches the use of serum (2, 7, 19, 27,37, 60) or plasma (claims 3,8, 18, 28, 36, 61) (see title, abstract). Gocke teaches peripheral blood (claims 81, 82, 84, 86, 90, 92, 96); plasma or serum is easily accessible and amenable for DNA amplification (see column 2, lines 54-55). Gocke further teaches detection colon cancer (claims 14, 32,68), breast cancer (claims 15,33, 69) or brain cancer (claims 16, 34, 70) by this method (see column 30, line 55-58). Gocke et al further teaches that many studies have used nucleic acid amplification to detect intracellular DNA extracted from circulating cells in blood (see column 2, line 56-60). Gocke teaches use of plasma or serum allows rapid and timely extraction and sensitive detection of extracellular tumor associated or extracellular mutated oncogenic DNA (see column 3, lines 60-63).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Soegnas method of detecting markers D12S1657, D12S393, D12S1706, and D12S346 by use of peripheral blood, plasma, or serum as taught by Gocke, because Gocke teaches plasma or serum is easily accessible and amenable for DNA amplification. The ordinary artisan would be motivated to improve Soegnas method of detecting including D12S1657, D12S393, D12S1706, and D12S346 markers by use of plasma or serum as taught by Gocke,

because Gocke teaches plasma or serum is easily accessible and amenable for DNA amplification. The ordinary artisan would further be motivated because, Gocke teaches use of plasma or serum allows rapid and timely extraction and sensitive detection of extracellular tumor associated or extracellular mutated oncogenic DNA. Thus as Gocke and teaches methods of nucleic acid analysis by PCR amplification as taught by Soegnas the artisan would have a reasonable expectation of success. The combination of Soegans and Gocke would have resulted in a method of detecting the presence or absence of D12S1657, D12S393, D12S1706, and D12S346 markers in acellular DNA from blood, serum, or plasma and from this detection allow the detection of melanoma, prediction of efficacy of adrianmycin, and responsiveness to adrinmycine. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Response to Arguments

The response on page 19 asserts correctly that Soegnas does not teach analyzing and detecting of DNA markers existing in accellular DNA, however Soegnas was not relied on for teaching analyzing and detecting DNA markers existing in extracellular DNA.

The response further correctly asserts that Gocke does not teach detection of D12S1657, D12S393, D12S1706, and D12S346 DNA markers, however Gocke was not relied upon for the teaching of these markers.

The response further asserts that the combination of Soegnase and Gock would not result in a reasonable expectation of success. First, MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding the reasonable expectation of success of the combination of Soegnas in view of Gocke are arguments that have not supported by adequate evidence. Further as both piece of art suggest analysis by PCR, the propose using the same method, that is well accepted.

The response further suggests that the teachings of Gocke (detection of nucleic acid in accellular DNA) are genus that are not obvious over the species (iD12S1657, D12S393, D12S1706, and D12S346) taught by Soegnas due to the In re Baird, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). This argument has been thoroughly reviewed but is not considered persuasive, as the instant claims are to methods, however Baird is drawn to genus/species analysis of compositions. Thus this argument is moot with respect to the instant claims.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 17, 26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7, 9, 11, 17, and 23 of copending Application No. 10/809965. Although the conflicting claims are not identical, they are not patentably distinct from each other because although not identical, they are co-extensive in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 of instant invention is drawn to detecting any markers of 12q22-23 from an accellular sample. Claim 1 and 17 of '965 are drawn to detecting markers from an accellular sample.

Claim 6 of instant application is drawn to detection of LOH. Claim 7 of '965 is drawn to detection of LOH.

Claim 17 of instant application is drawn to staging cancer by LOH detection. Claim 9 and 20 of '965 are drawn to staging cancer by LOH.

Claim 26 of instant application is drawn to prognosing cancer by LOH. Claim 11 and 23 are drawn to prognosing cancer by LOH.

Response to Arguments

The applicant asserts in the response of 11/19/2007, that instant claims are allowable other than for the double patenting rejections applicant will submit appropriate terminal disclaimers. This rejection is maintained.

Summary

No claims are allowed.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

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